REMARKS

Applicant's counsel thanks the Examiner for the careful consideration given the application.

Claims 26-38 are currently pending. These claims have been rejected under Section 35 USC §103(a).

The prior art documents cited by the Examiner are:

- D1: U.S. Patent N.° 6,458,981 (US'981)
- D2: U.S. Patent N.° 6,461,664 (US'664)
- D3: U.S. Patent N.° 4,020,158 (US'158)

The present invention is directed to:

- Claims 26 to 29: refer to a method for preparing an integrator and the human use thereof;
- Claim 30 to 32: refer to a method for preparing a metal chelate between an alkali metal or alkaline-earth metal salt of Methionine Hydroxy Analogue (MHA) and a soluble iron (II) salt;
- Claims 33 to 38: refer to a composition comprising complexes of formula [MHA:M(III)], wherein M(III) is: iron (III) or chrome (III).

First of all, it is very important to realize that Methionine Hydroxy Analogue (abbreviated as MHA) is not an amino acid.

The amino acid Methionine should not be confused with a Methionine Hydroxy Analogue.

Pages from The Merck Index 13th edition are herewith enclosed for prompt reference – see Annexes 1 and 2.

Methionine CAS Reg. N.° 63-68-3: CH_3-S-CH_2-CH_2-CH(**NH_2**)-COOH

MHA CAS Reg. N.° 583-91-5: CH_3-S-CH_2-CH_2-CH(**OH**)-COOH

PRIOR ART DOCUMENTS

D1 (US'981) relates to a composition and a method for preparing amino acid chelates.
The composition is prepared by reacting a calcium oxide or hydroxide, an amino acid and a soluble metal sulfate salt in an aqueous environment.

The amino acid is selected from the group consisting of: Methionine, Alanine, Arginine, etc., and combinations thereof (col. 6, lines 15-20).

The soluble metal sulfate salt is selected from the group consisting of copper sulfate, zinc sulfate, ferrous sulfate etc., ferric sulfate and chromic sulfate and combinations thereof (col. 6, lines 25-30.

A reaction mechanism of the process of US'981 comprises the following two steps (col. 6, lines 32-60):

Step a): involves the reaction of one or more amino acids with a calcium oxide or hydroxide in an aqueous environment forming a calcium amino acid chelate or complex product.

Step (b): involves the reaction of one or more soluble metal sulfate salts with the calcium amino acid chelate or complex product formed in Step a).

From the above reaction mechanism the following components are produced (col. 5, lines 60-62):
- a positively charged metal amino acid chelate having a hydroxide counter ion,
- a calcium sulfate salt, and optionally,
- water.

Note that the calcium reacts with the sulfate anion to form an inert and highly insoluble calcium sulfate precipitate (col. 6, lines 41-42). One can see said insoluble calcium sulfate precipitate as a sort of "by-product".

US'981 does **not** teach or suggest that Methionine Hydroxy Analogue (MHA) can be used instead of the amino acid Methionine.

US'981 does **not** teach or suggest the use of Methionine Hydroxy Analogue metal chelates for preparing an integrator which is administered to human beings or animals suffering from a deficiency of metal oligoelements such as Mg, Ca, Mn, Co, Cu, Zn and Fe as claimed in the present claims 26-29.

US'981 does **not** teach or suggest a method as claimed in the present claim 30 in which an alkali metal or alkaline-earth metal salt of methionine hydroxy analogue is reacted with a soluble iron (II) salt in water in a one step process (claim 30):

$2\ CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}CH(\mathbf{OH})\text{-}COO^{(-)}Na^{(+)} + FeSO_4$ in aq. solution $\rightarrow$

$(CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}CH(\mathbf{OH})\text{-}COO)_2Fe + Na_2SO_4$

Finally, US'981 does **not** teach or suggest a composition comprising water and a complex of the general formula [Methionine Hydroxy Analogue:M(III)] as claimed in the present claims 33 to 35.

Also US'981 does **not** teach or suggest the use of said composition as an integrator to be administered to human beings or monogastric or polygastric animals.

Note that the Methionine Hydroxy Analogue metal chelates of the present invention are not positively charged and therefore said chelates do not need the presence of a counter ion such as for example a hydroxide.

D2(US'664) teaches feed additive for agro-zootechnical use, in particular for alimentary use in the zootechnical sector, consisting of a chelate obtained by the reaction of MHA with the carbonate of bivalent metal. The product is stable and effective in improving the main growth factors of the animals.

D2 does **not** teach or suggest a method for preparing an integrator comprising at least one metal chelate as claimed in the present claims 26 and 27.

D2 does **not** teach or suggest that the integrator is administered to human beings suffering from a deficiency of metal oligoelements such as Mg, Ca, Mn, Co, Cu, Zn and Fe as claimed in the present claim 28.

D2 does **not** teach or suggest that the integrator is administered to monogastric or polygastric animals as claimed in the present claim 29.

D3(US'158) teaches that the levels of nutritionally essential metals in biological tissue are improved by administering corrective dosages of the metal found to be deficient, the metal being administered in the form of metal proteinates.

D3 relates to a method of raising the levels of essential bivalent metals (only bivalent metals, D3 does not show or suggest trivalent metals such as Fe(III) and Cr(III)) in the tissues of animals which comprises administering to said animal an effective amount of exogenously synthesized metabolically assimilable metal proteinates (col. 11, lines 14-19).

Said metal proteinates being in the form of chelates of said bivalent metals with one or more protein hydrolysates selected from the group consisting of polypeptides, peptide and amino acids (col. 11, lines 20-22).

Said proteinates are formed by dissolving salts of said metals in an aqueous solution containing the protein hydrolysates and adding sufficient base to raise the pH to a value from 7.5 to 10 to precipitate said metal proteinates (col. 11, lines 23-27).

Please note that D3 considers "the metal content of skin and feathers as an indicator as to dietary deficiencies", col. 1, lines 27-31.

Col. 1, lines 32-39 recites " the present invention provides a method for increasing the uptake of essential bivalent metals into animal tissues and diagnosing and treating metal deficiencies in animals by analyzing skin, feathers, hair and comparing the metal content with values obtained from similar tissue specimens derived from healthy and productive control animals.".

Essential bivalent metals are in the form of exogenously synthesized metabolically assimilable metal chetales, col. 2, lines 53-56.

Col. 3, lines 26-30 recites "It has been found that a chelate of the metal with a protein hydrolysate or naturally occurring amino acid renders the metal more readily assimilable than if the metal were in an inorganic form or in a different organic form.".

US'158 does **not** teach or suggest the use of Methionine Hydroxy Analogue (MHA) at all.

US'158 does **not** teach or suggest the use of Methionine Hydroxy Analogue (MHA) metal complexes instead of said metal proteinates.

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The Examiner states that Claims 26-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over D1 (U.S. Patent No. 6,458,981) in view of D2 (U.S. Patent No. 6,461,664) and D2 (U.S. Patent No. 4,020,158). Applicant respectfully disagrees.

According to the Examiner's position D1 represents the closest state of the art for all claims 26-38.

With reference to Claims 26-29

The difference between claim 26 and D1 is an integrator comprising at least one Methionine Hydroxy Analogue metal chelates to be administered to human beings or animals suffering from a deficiency of metal oligoelements such as Mg, Ca, Mn, Co, Cu, Zn and Fe.

The technical effects of the above difference is demonstrated in the *vivo* tests reported in the present application at page 11, line 2.

In practice the method of claim 26 allows one to prepare an integrator which can be administered to human beings and animals suffering from a deficiency of metal oligoelements.

In *vivo* test for monogastric animals (pigs) page 11, line 6, to page 13, line 9.

As is known, pigs are one of the man-closest animal models and as such they are often used as models for evaluations and studies in the human field (page 13, lines 7-9).

The results of the chemical analyses carried out on the samples are shown in Table 1 (page 14).
The pigs were sacrificed at an average weight of 16.2 kg. The average daily weight increase was of 324 g.
As can be inferred from the data shown in Table 2 (page 14) concerning daily zinc retention of the two different sources, the integration of zinc chelate was retained by the organism 26% more (P=0.07) than the integration with zinc sulfate.
Table 3 (page 14) shows the data concerning the effect of the zinc source on the content of zinc, copper and iron in liver, kidney and brain and, therefore, on the interaction with said elements present in the diet under inorganic form. As a matter of fact, it is known about the interaction exerted by said free ions by reducing one the absorption of the other.
The content of said three minerals in liver was not affected by the diet and therefore by the zinc source. Average values were 296 mg/kg for zinc, 63 mg/kg for copper and 220 for iron. Conversely, kidney showed a higher content of zinc (+18%, P=0.07), of iron (+36%, P<0.01) and of copper (+36%, P=0.12), and did not reach only for the latter value the threshold of statistical significance, though it showed a tendency towards an increase in the retention of said metal element.
In brain there was a tendency towards a higher content of zinc (+13%), of copper (+20%), of iron (+25%).
The obtained results point out a higher bioavailability of the metal element in chelated form with respect to inorganic sources such as sulfates, and further a lower interaction with other ions, which results in a higher retention of the latter.

In *vivo* test for polygastric animals (meat cattle) page 13, line 10, to page 14, line 1.

Two groups of female Charolaise calves (30 months old) comprising 6 animals each, with an average starting weight of 567 kg (Control and of 565 kg (Test), were fed for 90 days with the same diet. The only difference was that the Control group was administered zinc carbonate and the Test group zinc chelate according to the present invention. Daily ingestion was of 22 kg/animal and the total daily supply of zinc element was of 700 mg.
Living weight at test beginning and end, dead weight and slaughtering yield were determined for each animal. Data are shown in Table 4 (Page 15).
Animals fed with zinc chelate with respect to those fed with zinc carbonate have a significantly higher final weight (652 kg vs. 642 kg, p<0.05), a significantly higher daily weight increase (1,039

g vs. 934 g, $p<0.05$), a significantly higher carcass weight (377 kg vs. 366 kg, $P<0.01$), and a significantly higher yield (57.83% vs. 57.03%, $p<0.01$). Data are shown in Table 4 (page 15). The effect due to the presence of zinc chelate in the ratio administered to animals is shown in Table 5 (page 16).
Said results show an evident improvement of the aforesaid zootechnical performances of zinc chelate with respect to inorganic sources of said element.

On the other hand D2 does **not** teach or suggest:

- a method for preparing an integrator comprising at least one metal chelate as claimed in the present claims 26 and 27,
- an integrator to be administered to human beings suffering from a deficiency of metal oligoelements such as Mg, Ca, Mn, Co, Cu, Zn and Fe as claimed in the present claim 28,
- an integrator to be administered to monogastric or polygastric animals as claimed in the present claim 29.

Also D3 does **not** teach or suggest:

- the use of Methionine Hydroxy Analogue (MHA),
- the use of Methionine Hydroxy Analogue (MHA) metal complexes instead of said metal proteinates.

In view of the above the skilled person is not able to combine D1 with D2 and D3 to obtain a method as claimed in claims 26-29.

Therefore, the Examiner's objection under 35 U.S.C. 103(a) should be considered overcome and claims 26-29 patentable.

With reference to Claims 30-32

The difference between claim 30 and D1 is a method for preparing a metal chelate of formula $(CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}CH(\mathbf{OH})\text{-}COO)_2Fe\bullet 2H_2O$ by reacting of an alkali metal or alkaline-earth metal salt of Methionine Hydroxy Analogue with a soluble iron (II) salt in water.

The technical effect of the above method is given by the fact that the method is a one step process and the Methionine Hydroxy Analogue metal chelate of iron (II) obtained is stable and pure (see page 7, lines 5-26 in the present application).

D2 shows a process for preparing $(CH_3\text{-}S\text{-}CH_2\text{-}CH_2\text{-}CH(\mathbf{OH})\text{-}COO)_2Fe\bullet nH_2O$ starting from Methionine Hydroxy Analogue and iron carbonate.

The reaction process of D2 is slightly exothermic with evolution of CO_2 gas.

It is submitted that D3 does not represent a relevant prior art document for claims 30-32.

In view of the above the skilled person is not able to combine D1 with D2 and D3 to obtain a method as claimed in claims 30-32.

Therefore, the Examiner's objection under 35 U.S.C. 103(a) should be considered overcome and claims 30-32 patentable.

With reference to Claims 33-38

The difference between claim 33 and D1 is a composition comprising water and at least one complex of formula [Methionine Hydroxy Analogue : M(III)] wherein M(III) is iron (III) and chrome (III) with a molar ratio between MHA and M(III) equal or bigger than 2.

Stability constants for the various Fe/MHA complexes have been calculated with potentiometric titrations. The stability of iron (III) complexes is very high and chelated species form also at acid pH. Uncomplexed Fe3+ ions are present only at very low pH values (<2.5), whereas at higher pH values all iron (III) is complexed as chelated species metal/ligand = 1:2 (see page 14, lines 4-8).

Neither D2 nor D3 teach or suggest the use of trivalent metals.

Further see *in vitro* tests from page 8, line 28, to page 11, line 1, where Fe(III)/MHA (1:3) has been tested.

The results are shown in Figure 4, indicating the content of intracellular iron after 3 hours of treatment with Fe(III)/MHA and Fe(III)/NTA at different concentrations. Data are expressed in nmoles iron/filter.

As can be inferred from Figure 4, the passage of iron/MHA chelate from the apical environment, C, to the cell is higher than the one observed in the control.

Moreover, from Figure 5 (showing iron transport from apical environment C to basolateral environment D after treatment with two different concentrations of Fe(III)/MHA and Fe(III)/NTA) it can be inferred that the concentration of transported iron is comparable. Data are expressed in nmoles iron/filter.

Data shown in Figure 4 and 5 confirm that iron chelate is strongly absorbed by cells of intestinal microvilli and moves within blood flow.

From Figure 2 (showing TEER measurements) it can be inferred that intercellular links are unchanged, thus proving the non-toxicity of iron chelate towards cells, contrary to what happens in the case of unchelated iron such as ferrous sulfate.

Figure 3 shows the measurement of TEER 24 hours after the buffer solution at 5.5 containing iron/MHA or iron/NTA has been removed keeping the cells in culture. Said Figure 3 shows how iron chelate/MHA is stable within cells causing no toxic effect.

Finally, the tests show that MHA/M chelates according to the present invention are efficiently absorbed, stable within intestinal cells and non-toxic.
The results shown above support the use of said new chelates, both in solid form with iron (II), vanadium (IV) and/or vanadium (V) and molybdenum (V) and/or molybdenum (VI), and in liquid form in aqueous solution with iron (II) and (III) and chrome (III), for the preparation of metal integrators for human and animal nutrition.

In view of the above the skilled person is not able to combine D1 with D2 and D3 to obtain a composition as claimed in claims 33-38.

Therefore, the Examiner's objection under 35 U.S.C. 103(a) should be considered overcome and claims 33-38 patentable.

For all the foregoing reasons it is believed that the claims as now presented are patentable and in condition for allowance, which is respectfully requested.

If any fees are required by this communication which are not covered by an enclosed check, please charge such fees to our Deposit Account No. 16-0820, Order No. 37891.

Respectfully submitted,

PEARNE & GORDON LLP

By _____
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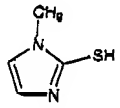
Date: 3-30-06

...vania. LD_{50} in adult male, female rats (mg/kg): 31, 32 orally (Gaines, Linder).

USE: Insecticide, acaricide.

6000. Methimazole. [60-56-0] 1,3-Dihydro-1-methyl-2*H*-imidazole-2-thione; 1-methylimidazole-2-thiol; 1-methyl-2-mercaptoimidazole; mercazolyl; thiamazole; Basolan; Danantizol; Favistan; Frenurox; Mercazole; Metazolo; Tapazole; Thiapazol; Thycapsol; Strumazol. $C_4H_6N_2S$; mol wt 114.17. C 42.08%, H 5.30%, N 24.54%, S 28.09%. Prepd by treating aminoacetaldehyde diethyl acetal with methyl isothiocyanate: Wohl, Marckwald, *Ber.* 22, 1354 (1889); from thiocyanic acid and N-substituted amino acetals: Jones *et al., J. Am. Chem. Soc.* 71, 4000 (1949). Metabolism: D. S. Sitar, D. P. Thornhill, *J. Pharmacol. Exp. Ther.* 184, 432 (1973). Comprehensive de-...tion: H. Y. Aboul-Enein, A. A. Al-Badr, *Anal. Profiles ...Subs.* 8, 351-370 (1979). Review of pharmacology and ...linical experience: D. S. Cooper, *N. Engl. J. Med.* 311, 1353-...62 (1984).



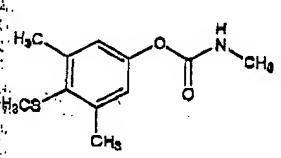
...Aniers from alc, mp 146-148°. bp 280° (some decompn). ...max (0.1*N* H_2SO_4): 211, 251.5 nm ($E^{1\%}_{1cm}$ 593, 1528). Freely ...water. Sol in alcohol, chloroform. Sparingly sol in ether, ...benzene.

...Methiodide. Jomezol.

...In cyanide-free silver electroplating.

...CAT: Antihyperthyroid.

6001. Methiocarb. [2032-65-7] 3,5-Dimethyl-4-(methylthio)phenol methylcarbamate; methylcarbamic acid 4-(methylthio)-3,5-xylyl ester; 4-(methylthio)-3,5-xylyl methylcarbamate; 4-methylthio-3,5-dimethylphenyl *N*-methylcarbamate; mercaptodimethur; metmercapturon; Bayer 37344; H-321; Mesurol. $C_{11}H_{15}NO_2S$; mol wt 225.31. C 58.64%, H ...N 6.22%, O 14.20%, S 14.23%. Prepn: E. Schegk *et al.*, GB 912895; *eidem*, US 3313684 (1962, 1967 both to ...E. Gilbert, J. A. Otto, US 3358012 (1967 to Allied). ...cidal activity: H. H. Crowell, *J. Econ. Entomol.* 60, ...(1967). Bird repellent properties: E.W. Schafer, R. B. ...*Wildl. Manage.* 35, 569 (1971). Toxicity study: T. ...*Toxicol. Appl. Pharmacol.* 14, 515 (1969).



...crystalline powder, mp 121.5°. Insol in water. Sol in ...solvents. Unstable in alk media. LD_{50} in male, female ...(mg/kg): 70, 60 orally (Gaines).

USE: Insecticide; molluscicide; bird repellent.

6002. Methiodal Sodium. [126-31-8] Iodomethanesulfonic acid sodium salt; sodium iodomethanesulfonate; Skiodan; Radiographol; Segosin; Diagnorenol. CH_2INaO_3S; ...243.98. C 4.92%, H 0.83%, I 52.01%, Na 9.42%, O ...S 13.14%. CH_2ISO_3Na. Prepd by the action of sodium ...methylene iodide at 70° in water-alcohol soln: Os...*et al.*, US 1842626 (1932 to Winthrop); from iodoform ...sulfite: Allardt, US 1867793 (1932 to Schering-Kahl...

...Slightly saline taste followed by sweetish aftertaste. ...sol in water (70 g/100 ml); slightly sol in alcohol (2.5 ...benzene, ether, acetone.

THERAP CAT: Diagnostic aid (radiopaque medium—uro-

6003. Methionic Acid. [503-40-2] Methanedisulfonic acid. $CH_4O_6S_2$; mol wt 176.17. C 6.82%, H 2.29%, O 54.49%, S 36.40%. $CH_2(SO_3H)_2$. Prepn from methane + sulfur trioxide: Snyder, Grosse, US 2493038 (1950 to Houdry Process); by H_2SO_4 oxidation of acetic acid: Schwab, Neuwirth, *Ber.* 90, 567 (1957); from $MeSO_3H$ + SO_3: Crowder, Gilbert, US 2842589 (1958 to Allied Chem.). Prepn of aluminum salt: Christian, Jenkins, *J. Am. Pharm. Assoc.* 39, 633 (1950); US 2504107 (1950 to Purdue Res. Found.).

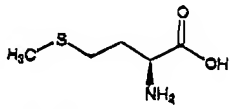
Crystals, mp 96-100°.

Aluminum salt. $C_2H_6Al_2O_{12}S_2$. Crystals from water + alcohol. Hygroscopic. Soly in water at 27°: 69 w/v. pH of 5% aq soln = 3.5.

USE: Antiperspirant.

THERAP CAT: Aluminum salt as topical astringent.

6004. Methionine. [63-68-3] L-Methionine; Met; M; 2-amino-4-(methylthio)butyric acid; α-amino-γ-methylmercaptobutyric acid; (*S*)-2-amino-4-(methylthio)butanoic acid; γ-methylthio-α-aminobutyric acid; Acimethin. $C_5H_{11}NO_2S$; mol wt 149.21. C 40.25%, H 7.43%, N 9.39%, O 21.44%, S 21.49%. Essential amino acid for human development. Universal translation start signal although usually missing from mature protein. Isoln from casein: J. H. Mueller, *Proc. Soc. Exp. Biol. Med.* 19, 161 (1922). Early chemistry and biochemistry: *Amino Acids and Proteins*, D. M. Greenberg, Ed. (Charles C. Thomas, Springfield, IL, 1951) 950 pp., *passim*; J. P. Greenstein, M. Winitz, *Chemistry of the Amino Acids* vols. 1-3 (John Wiley and Sons, Inc., New York, 1961) pp. 2125-2155, *passim*. Determn and distribution in non-protein fractions: J. Giovanelli, S. H. Mudd, *J. Biochem. Biophys. Methods* 11, 1 (1985). GC-MS determn in biological fluids: S. P. Stabler *et al., Anal. Biochem.* 162, 185 (1987). Evaluation as tracer in cancer imaging in mice: R. Kubota, *J. Nucl. Med.* 36, 484 (1995). Clinical evaluation in acetaminophen overdose: A. N. Hamlyn *et al., J. Int. Med. Res.* 9, 226 (1981). Clinical use as radiolabel in hyperparathyroidism: P. Hellman *et al., Surgery* 116, 974 (1994). Review of metabolism and clinical significance in man: L. D. Fleisher, G. E. Gaull, *Clin. Endocrinol. Metab.* 3, 37-55 (1974); and in carcinogenesis: T. L. Gatton-Umphress, *Hosp. Pract.* 28, 83-90 (1993). Review of toxicity: N. J. Benevenga, *J. Agric. Food Chem.* 22, 2-9 (1974). Review of biosynthesis: I. G. Old *et al., Prog. Biophys. Mol. Biol.* 56, 145-185 (1991). Review as translation start signal: T. Meinnel *et al., Biochimie* 75, 1061-1075 (1993).



Minute hexagonal plates from dil alc, mp 280-282° (dec, sealed capillary). $[\alpha]_D^{25}$ −8.11° (c = 0.8). $[\alpha]_D^{20}$ +23.40° (c = 5.0 in 3*N* HCl). Sol in water, but the crystals are somewhat water-repellent at first. Sol in warm, dil alcohol. Insol in abs alcohol, ether, petr ether, benzene, acetone.

D-Form. [348-67-4] Converted by deamination, followed by transaminadon with resultant inversion to the L-form. Comparative study with L-form of metabolism in plants: M. Pokorny *et al., Phytochemistry* 9, 2175 (1970). Evaluation in parenteral nutrition: K J. Printen *et al., Am. J. Clin. Nutr.* 32, 1200 (1979). *Review:* L. D. Stegink, D-Amino Acids in *Clin. Nutr. Updates: Amino Acids*, H. L. Greene *et al.*, Eds. (American Medical Association, Chicago, IL, 1977) pp 198-206. $[\alpha]_D^{25}$ +8.12° (c = 0.8). $[\alpha]_D^{25}$ −21.18° (c = 0.8 in 0.2*N* HCl).

DL-Form. [59-51-8] Racemethionine; Banthionine; Dyprin; Lobamine; Metione; Pedameth; Urimeth. Platelets from alc, mp 281° (decompn). d 1.340. pK_1 2.28; pK_2 9.21. pH of 1% aq soln 5.6-6.1. R_f value 0.77. Soly in water (g/l) at 0°: 18.18; at 25°: 33.81; at 50°: 60.70; at 75°: 105.2; at 100°: 176.0. Sol in dil acids, alkalies. Very slightly sol in 95% alcohol. Insol in ether.

THERAP CAT: Hepatoprotectant; antidote (acetaminophen poisoning); urinary acidifier.

THERAP CAT (VET): Nutritional supplement; urinary acidifier.

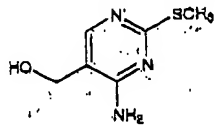
Annex 2

6005. Methionine Hydroxy Analog. [583-91-5] 2-Hydroxy-4-(methylthio)-butanoic acid; 2-hydroxy-4-(methylthio)-butyric acid; Alimet. $C_5H_{10}O_3S$; mol wt 150.20. C 39.98%, H 6.71%, O 31.96%, S 21.35%. $CH_3SCH_2CH_2CH(OH)COOH$. Prepn (not claimed) and use as poultry feed additive: E. S. Blake, R. J. Wineman, US 2745745 (1956 to Monsanto). HPLC determn in feeds: A. Baudichau *et al., J. Sci. Food Agr.* 38, 1 (1987). Use as a feed additive for livestock: A. Papas *et al., J. Nutr.* 104, 653 (1974); A. K. Clark, A. H. Rakes, *J. Dairy Sci.* 65, 1493 (1982); D. H. Reifsnyder *et al., J. Nutr.* 114, 1705 (1984). Efficacy of calcium salt vs free acid: K. P. Baebel, D. H. Baker, *Poultry Sci.* 61, 1167 (1982).

Calcium salt. MHA. $C_{10}H_{18}CaO_6S_2$; mol wt 338.46.

USE: Dietary supplement in livestock.

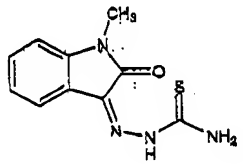
6006. Methioprim. [588-36-3] 4-Amino-2-methylthio-5-pyrimidinemethanol; 4-amino-2-methylmercapto-5-pyrimidinemethanol; 4-amino-5-hydroxymethyl-2-methylthiopyrimidine. $C_6H_9N_3OS$; mol wt 171.22. C 42.09%, H 5.30%, N 24.54%, O 9.34%, S 18.73%. Synthesis starting with ethyl ethoxyethylenecyanoacetate: Ulbricht, Price, *J. Org. Chem.* 21, 567 (1956).



Needle-like prisms from benzene, mp 126-127°.

USE: Tumor antagonist in mice.

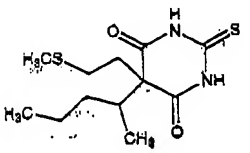
6007. Methisazone. [1910-68-5] 2-(1,2-Dihydro-1-methyl-2-oxo-3*H*-indol-3-ylidene)hydrazinecarbothioamide; 1-methylindole-2,3-dione 3-thiosemicarbazone; *N*-methylisatin 3-thiosemicarbazone; BW-33-T-57; Marboran; Viruzona. $C_{10}H_{10}N_4OS$; mol wt 234.28. C 51.27%, H 4.30%, N 23.91%, O 6.83%, S 13.69%. Prepn: Bauer, Sadler, *Brit. J. Pharmacol.* 15, 101 (1960); GB 975357 (1964 to Wellcome Found.).



Crystals from butanol, mp 245°.

THERAP CAT: Antiviral.

6008. Methitural. [467-43-6] Dihydro-5-(1-methylbutyl)-5-[2-(methylthio)ethyl]-2-thioxo-4,6(1*H*,5*H*)-pyrimidinedione; 5-(1-methylbutyl)-5-[2-(methylthio)ethyl]-2-thiobarbituric acid; 5-(2-methylthioethyl)-5-(2-pentyl)-2-thiobarbituric acid. $C_{12}H_{20}N_2O_2S_2$; mol wt 288.43. C 49.97%, H 6.99%, N 9.71%, O 11.09%, S 22.23%. Prepn: Zima, Von Werder, US 2802827 (1957 to E. Merck).

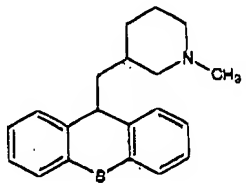


Sodium salt. [730-68-7] Methiopurate; AM-109; Sch-3132; Neraval; Thiogenal. $C_{12}H_{19}N_2NaO_2S_2$; mol wt 310.42. Very hygroscopic, yellow crystals. Slight odor of mercaptans. Freely sol in water. pH of a 10% aq soln ~9.5. Water solns are unstable as evidenced by a deepening of color and formation of a cloudy precipitate upon autoclaving and exposure to li... The addition of sodium carbonate has a stabilizing effect ... prevents precipitation for about 24 hrs: Irwin *et al., J. Pharmacol. Exp. Ther.* 116, 317 (1956).

Caution: May be habit forming: 21 CFR, 329.1 and ... controlled substance (depressant): 21 CFR, 1308.13.

THERAP CAT: Sedative, hypnotic.

6009. Methixene. [4969-02-2] 1-Methyl-3-(9*H*-thioxanthen-9-ylmethyl)piperidine; 9-(*N*-methyl-3-piperidylmethyl)-thioxanthene. $C_{20}H_{23}NS$; mol wt 309.48. C 77.62%, H 7.49%, N 4.53%, S 10.36%. Anticholinergic. Prepn: Cavierzel ... *Pharm. Acta Helv.* 33, 447 (1958); J. Schmutz, US 2905... (1959 to Wander). Metabolism and toxicity study: H. ... *et al., Arzneimittel-Forsch.* 14, 89 (1964). Crystal structure: S. C. Chu, *Acta Crystallogr.* B28, 3625 (1972). Spectrometric determn: F. Belal *et al., Anal. Chim. Acta* 235, ... (1991). Comprehensive description: E. M. Abdel-Moety ... *Anal. Profiles Drug Subs. Excip.* 22, 317-358 (1993).

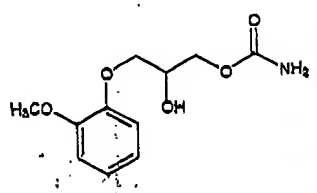


Slightly yellow viscous liquid, $bp_{0.07}$ 171-175°. Insol in ...

Hydrochloride monohydrate. [7081-40-5] ... Methixart; Trest; Tremonil; Tremadil; Tremarit; Cho... Methyloxan. $C_{20}H_{23}NS.HCl.H_2O$; mol wt 363.95. Flakes from ether, mp 215-217°. uv max (dil HCl): 268 nm (ε 10250). ... in water, alcohol, chloroform. Insol in ether.

THERAP CAT: Antiparkinsonian.

6010. Methocarbamol. [532-03-6] 3-(2-Methoxyphenoxy)-1,2-propanediol 1-carbamate; 3-(*o*-methoxyphenoxy)-2-hydroxypropyl 1-carbamate; 2-hydroxy-3-(*o*-methoxyphenoxy)propyl 1-carbamate; guaiacol glyceryl ether carbamate; AHR-85; Neuraxin; Miolaxene; Lumirelax; Eroflex; ... Robamol; Treumacut; Tresortil; Relestrid; Robaxin. ... NO_5; mol wt 241.24. C 54.77%, H 6.27%, N 5.81%, O ... Prepn from 3-(*o*-methoxyphenoxy)-2-hydroxypropyl chloro... bonate: Murphey, US 2770649 (1956 to A. H. Robins). ... prehensive description: S. Alessi-Severini *et al., Anal. Pro... Drug Subs. Excip.* 23, 371-399 (1994).



Crystals from benzene, mp 92-94°. uv max (water) ... nm ($E^{1\%}_{1cm}$ 298, 94). log P −0.06. Soly in water at 20° ... 100 ml. Sol in alcohol, propylene glycol. Sparingly sol ... roform. Practically insol in *n*-hexane.

THERAP CAT: Muscle relaxant (skeletal).

THERAP CAT (VET): Muscle relaxant (skeletal).

6011. Methohexital Sodium. [22151-68-4] ... (1-methyl-2-pentynyl)-5-(2-propenyl)-2,4,6(1*H*,3*H*,5*H*)-... idinetrione sodium salt; 5-allyl-1-methyl-5-(1-methyl-... tynyl)barbituric acid sodium salt; *α-dl*-1-methyl-5-(1-... pentynyl)-5-allylbarbituric acid sodium salt; *α-dl*-1-methyl-... allyl-5-(1-methyl-2-pentynyl)barbituric acid sodium ... methohexitone sodium; Brevital; Brevital Sodium; Brev... Sodium; Brietal Sodium. $C_{14}H_{17}N_2NaO_3$; mol wt 28...